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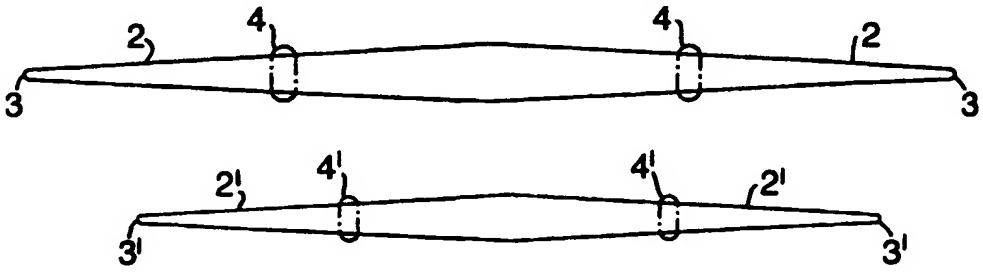
(54) Title: OCULAR INSERT



(57) Abstract: A flexible ocular insert device adapted for the controlled sustained release of a drug upon insertion into the upper or lower fornix of the eye, said device comprising an elongate body of a polymeric material including two end portions said body containing a pharmaceutically active ingredient, said device having a length of at least 8 mm and a maximum diameter not exceeding 1.9 mm, wherein said device is sufficiently flexible to allow it to bend along the curvature of the eye within the upper or lower fornix upon being positioned so that the longitudinal axis of said device is generally parallel to the transverse diameter of the eyeball, the device does not extend onto any visible portion of the eyeball, and in which each of said end portions is tapered towards the extremities of the device.

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OCULAR INSERT

This invention is concerned with improvements in or relating to ocular insert devices.

Various diseases of the eye are commonly treated by frequent daily application of ophthalmic drugs for example in the form of eye drops or ointment. While this is suitable and convenient in some cases, it can be a serious disadvantage that the drug is not present in the eye in a continuous manner. Furthermore, applying drops or ointment can be unpleasant and patient compliance is often an issue. With a view to overcoming this disadvantage it has been previously proposed, for example, in U.S. Patent No. 3,416,530 of R.A. Ness assigned to Alza Corporation and subsequent patents of Alza Corporation to provide a flexible ocular insert device adapted for the controlled sustained release of the drug.

It is often very beneficial treat the eye with two or more drugs simultaneously. However, the problems associated with conventional methods of administration are compounded if two separate applications of drops or ointment must be made. Mixtures of drugs, which would allow a single application to deliver multiple drugs, require lengthy approval procedures, and for this reason are not commonly developed. It has been proposed to provide an ocular insert, which delivers a mixture of drugs to allow multiple drug delivery. This still requires an approval process, though, and it is also difficult to optimise the release kinetics for each drug.

In U.S. Patent No. 3,828,777 of R.A. Ness assigned to Alza Corporation it is stated that an ocular insert can be fabricated in any convenient shape for comfortable retention in the conjunctival sac of the eye and that the marginal outline can be ellipsoid, doughnut-shape, bean-shape, banana-shape, circular or rectangular; and in cross section it can be doubly convex, concavoconvex, or rectangular. It is suggested however that the original cross-sectional shape of the device is not of controlling importance. However, these previously proposed devices have in practice met with no more than limited success because most of the proposed shapes and sizes were not suitable for placement in the narrow upper and lower fornices. Also, previous devices

have tended not to remain in place in the eye and have at times caused irritation to the patient during use.

U.S. Patent No. 4,186,184 to A. Zaffaroni discloses that the length of an insert device should be from 2 to 20mm, its width 1 to 15mm and its thickness 0.1 to 4mm. A wide variety of shapes are disclosed including ellipsoid, doughnut, bean, banana and square shapes.

U.S. Patent No. 3,828,777 to Ness discloses an ocular device which is inserted in that portion of the eye bounded by the surfaces of the bulbar conjunctiva of the sclera of the eyeball and the palpebral conjunctiva of the lid. Such placement of the device would, however, be subject to eye movement and would not provide an anchored position such as is obtained in the present invention. Movement of the device causes pain, irritation, foreign body sensation and watering.

U.S. Patent No. 4,343,787 to Katz discloses water soluble inserts for the eye in which broad dimensional ranges of sizes and shapes are employed. There is no description of an insert of a specific size and shape to allow it to be retained in the fornix portion of the eye.

U.S. Patent No. 4,135,514 to Zaffaroni et al. relates to osmotic drug delivery devices which can be used for the administration of ocular drugs. A wide variety of shapes and sizes is disclosed.

EP-A-0 033 042 to Merck and Co., Inc. discloses ocular inserts which can take any of a variety of shapes, one of which may be an extruded rod. There is no description, however, of a device having dimensions which make it suitable for insertion into the fornix so as to be retained therein for 7 days or longer.

U.S. Patent No. 4,730,013 to Bondi et al. discloses ocular inserts intended to overcome the problem of blurred vision arising from the use of particular insert materials. The maximum length of 5mm employed by Bondi et al. is considerably smaller than the range of dimensions employed in the present invention. It is disclosed in this patent that a device with a length of 5mm falls well below the minimum length required for retention in the eye of humans for 7 days or more.

EPO 0 251 680 to IOLAB, Inc. discloses a device for controlled drug release

to the eye, in which an external matrix rapidly soluble in body fluids and having bioerodible microparticles containing the drug are positioned in the upper or lower conjunctival cul-de-sac of the eye. There is no description of a device which is retained in the eye for seven days or longer, or of the specific shape and dimension of the device of the invention for placement in the upper or lower fornix.

U.S. Patent No. 3,845,201 to Haddad et al. discloses an ocular device for insertion in the cul-de-sac of the conjunctiva. The device may be any of various shapes, preferably disc shaped.

U.S. Patent No. 4,164,559 to Miyata et al. discloses soluble device for drug delivery to the eye including collagen insert having an ovoid shape. The device is described as insertable into the inferior fornix. There is no description of a device having the dimensions employed in the present invention for retention of seven days or longer.

U.S. Patent No. 4,179,497 to Cohen et al. discloses water soluble inserts of various shapes for applying drugs to the cul-de-sac of the conjunctiva. Again there is no description of an insert having the specific dimensions of the invention.

In the use of a prior art device known as Ocusert, the subject of U.S. Patent No. 3,828,777 to Ness, the device is inserted into the conjunctival cul-de-sac. Either of two systems may be employed, with the Pilo-20 system measuring 5.7 x 13.4mm on its axes and 0.3mm in thickness and the Pilo-40 system measuring 5.5 x 13mm on its axes and 0.5mm in thickness. Various problems in retention and irritation which occurred in the use of this device are documented, for example, in the following publications: P. Sihvola et al., Practical problems in the use of Ocusert-pilocarpine delivery system, Acta Ophthalmol. (Copenh.), Dec. 1980, 58 (6), pp 933-937; S.E. Smith et al., Comparison of the pupillary, retractive and hypotensive effects of Ocusert-40 and pilocarpine eyedrops in the treatment of chronic simple glaucoma, Br. J. Ophthalmol., April 1979, 63(4) pp 228-232; and I.P. Pollack et al., The Ocusert pilocarpine system: advantages and disadvantages, South Med. J., October 1976, 69 (10), pp 1296-1298.

Other ocular inserts are described in the following literature reports: Urtti et al.

(1990) Controlled drug delivery devices for experimental ocular studies with timolol.1.In vitro release studies. Int. J. Pharm., 61, 235-240; and Urtti et al (1990) Controlled drug delivery devices for experimental ocular studies with timolol.2.Ocular and systemic absorption in rabbits. Int. J. Pharm., 61, 241-249. These reports describe the use of a permeable hollow tube (silicone) for ocular delivery. The tube has a diameter of 1.94mm which is outside the dimensions employed in the present invention. Also, the device was only observed in the eye for an 8 hour period.

EP-A-0,262,893 discloses a flexible ocular insert device adapted for the controlled sustained release of an ophthalmic drug into the eye, which comprises a body having a thin elongated circular cylindrical configuration, the device having for example a length of at least 8mm and a diameter not exceeding 1mm. The circular cylindrical body terminates at transverse end surfaces which may for example be planar or domed.

Previously published US-A-5,395,618 discloses a flexible ocular insert device adapted for the controlled sustained release of an ophthalmic drug upon insertion into the upper or lower fornix of the eye, said device comprising an elongated body of a polymeric material in the form of a rod or tube containing a pharmaceutically active ingredient and with at least two anchoring protrusions extending radially outwardly from said body, said device having a length of at least 8mm and a diameter including protrusions not exceeding 1.9mm, wherein said device is sufficiently flexible to allow it to bend along the curvature of the eye within the upper or lower fornix upon being positioned so that the longitudinal axis of said device is generally parallel to the transverse diameter of the eyeball, said device being of a size and configuration such that, upon insertion into the upper or lower fornix, the device does not extend onto any visible portion of the eyeball, said device being independent of movement of the eye and remaining out of the field of vision so as to be well retained in place and imperceptible by the patient over a prolonged period of use, said protrusions acting to minimise lateral movement of the device within the fornix, whereby the device when inserted into the upper or lower fornix can be retained therein for more than seven

days.

However, their retention is sub-optimal as far as comfort, adverse effects, movement within the fornix felt by the patient, foreign body sensation and irritation in general.

The present invention in a first aspect provides a flexible ocular insert device adapted for the controlled sustained release of a drug upon insertion into the upper or lower fornix of the eye, said device comprising an elongate body of a polymeric material including two end portions said body containing a pharmaceutically active ingredient, said device having a length of at least 8mm and a maximum diameter not exceeding 1.9mm, wherein said device is sufficiently flexible to allow it to bend along the curvature of the eye within the upper or lower fornix upon being positioned so that the longitudinal axis of said device is generally parallel to the transverse diameter of the eyeball, said device being of a size and configuration such that, upon insertion into the upper or lower fornix the device does not extend onto any visible portion of the eyeball, and in which each of said end portions is tapered towards the extremities of the device.

It has been found that such a flexible ocular insert device, is well retained in place and tolerated better by the patient over a period of use more prolonged than hitherto possible.

Whereas the flexible ocular insert device of US-A-5,395,618 permitted use of up to 7 or 14 days or longer in the upper fornix but usually less than 2 days in the lower fornix. Only between 14 to 47% of patients could retain the device in the upper fornix for 28 days or longer. The flexible ocular insert device of the present invention has been found to be retained by 72% of people for 28 days or longer when in the upper fornix and was retained in 36% of people for 28 days or longer when in the lower fornix.

The increased retention of the device fitted in the upper fornix means the device can be used to deliver drugs to the eyes to treat ailments requiring long term continuous treatment, ie one application for the treatment or prevention of infection or allergy or application every 1 to 3 months or longer for chronic diseases. The fact

that the device may be fitted and removed by the patients themselves into and out of the upper or lower fornix which, coupled with the high retention period in the fornices now allows the patient to fit a device of the present invention for self application of treatments that would previously have required an experienced person to fit and remove an ocular device to and from the fornices of a patient.

The device is designed to be inserted in the conjunctival folds of the upper or lower fornix at the junction between the palpebral conjunctiva of the upper or lower eyelid and bulbar conjunctiva of the eyeball, being held in position preferably in the extreme outer and inner end portions of the upper or lower fornix and prevented from moving downward or laterally respectively by the pressure and movement of the lid against the eyeball. When this insert was first developed, it was thought that the tapered end portions, at least in part, would lie between the upper or lower tarsus and the eyeball. Because of the taper, it was believed that the end portions would serve to prevent the device moving laterally in the fornix whilst also providing a reduced pressure on the eyeball compared to known prior art inserts when similarly positioned in the eyes.

More recently, it has been found that the tapered end portions are in fact contained entirely in the fornix, providing exceptional comfort for the user. The end region of the fornices of the adult eye have a width of approximately 0.4mm. It is not essential that the tips of the insert remain in the fornix, provided substantially all of the device is located within the fornix. However, for optimum comfort it is preferred that the device be retained entirely in the fornix and therefore that the tips of the device preferably have a maximum width of 0.4mm

The device may include optional radial protrusions acting, in use, to minimise lateral movement of device within the fornix.

The device may have protrusions extending outwardly a distance such that the overall diameter of the device including the protrusions is approximately 15 to 30% greater than the diameter of the body of said device. They may, for example, be positioned so as to be symmetrically disposed about the centre point of said body.

The protrusions, if present, are preferably toroidal or doughnut shaped around

the body to provide a ribbed configuration.

The body of device may include a cylindrical portion between the two end portions or be entirely formed by the two end portions, the end portions having a common base. The tapered end portions may each be in the form of a right circular cone or an oblique circular cone. Preferably, the apex of each end portion is rounded.

The tapered portions of the device may be straight or rounded, either at the tip only or for most or all of the taper. The maximum angle of the taper is preferably 15 degrees or less, more preferably 13.4 degrees or less, more preferably 10 degrees or less, still more preferably 7 degrees or less. In the case of a rounded or curved taper, the maximum angle is taken as the angle between the longitudinal centre line of the device and the line of maximum angle drawn between a tip of the device and the commencement of the taper of the corresponding tapered portion.

The length of each of the tapered portions is preferably 3mm or more.

The aspect ratio of overall diameter (maximum width) to length is preferably less than 0.20:1, more preferably less than 0.15:1, more preferably less than 0.1:1, still more preferably less than 0.07:1.

The tip or apex of each tapered portion may be rounded and may take the approximate form of a hemisphere; alternatively it may be a flat, truncated tip. The diameter or maximum width of the tip or apex preferably does not exceed 0.4mm, and is more preferably between 0.1 and 0.4mm.

The cross section of the device may be circular, oval, polygonal, etc. It is preferred that the aspect ratio of the overall shape of the cross section be approximately 1:1, although this is not essential and indeed the cross section may vary along the length of the device.

The length of the device is conveniently from 8 to 25mm for use in the lower fornix to suit the eyes of different sizes such as infants, children and adults, or from 8 to 35mm for use in the upper fornix to suit the eyes of different sizes such as infants, children and adults.

The overall diameter or maximum width of individual devices including protrusions is preferably from 0.5 to 1.9mm to suit the eyes of different sizes such as

infants, children and adults.

The mechanism of drug release may be, for example, by diffusion through an outer wall of the device, osmosis, bioerosion, or diffusion including possible drug dissolution.

The polymeric material of the device may be, for example, a silicone elastomer, made of hydrogel components or be a methacrylate or hydroxymethacrylate based material.

In particular, the device is advantageously inserted so as to fit within the upper or lower fornix by restriction of the cross sectional dimensions of the device to allow it to slip into this position and then with a length that provides for anchoring the device across the fornix. Two or more protrusion elements, when present, extend radially outwardly from the core to minimise lateral movement when the device is positioned within the fornix. By locating the device within the fornix, the device is imperceptible to the patient, through restriction of the device to a specific size range and shape, with the upper limit not being governed by the geometric space limitation of the whole eye, and by placement specifically within the fornix, not simply within the conjunctival cul-de-sac. In addition, the retention of the present insert device is independent of the movement of the eye or the lid by virtue of the fornix anatomy. In contrast, a device placed anywhere on the bulbar conjunctiva would be subject to eye and or lid movement and cause discomfort to the patient.

The insert device of the present invention must be positioned precisely and remain anchored in the upper or lower fornix, known also as the superior conjunctival fornix or the inferior conjunctival fornix, as distinct from the positioning of other kinds of devices anywhere in the conjunctival cul-de-sac. The device of the present invention must be flexible to allow it to bend along the curvature of the eye within the fornix. In particular, such flexibility must be sufficient to allow it to bend in the upper or lower fornix upon being positioned so that the longitudinal axis of the device is generally parallel to the transverse diameter of the eyeball.

The present insert device is imperceptible by the patient when anchored properly in the fornix, whereas prior art devices are perceived as foreign bodies.

Upon proper positioning in the fornix, the present insert device is independent of eye or lid movement and does not move when the eye or lid moves. The conical end portions improve retention in the required position whilst at the same time reducing adverse effects so leading to improved retention characteristics. The device of the present invention also remains out of the field of vision. In addition, it can be placed and held in position without interference during surgical procedures.

The length of the present insert device is also critical to the anchoring process in the fornix. The length of the device is related to the size of the eye, hence the optimum length for the human adult is 25mm, for children is about 15 to 18mm and for newborn babies is 10mm in length.

In general, for adults, the lengths of the upper fornix and lower fornix are about 45 to 50mm and 35 to 40mm respectively. Thus an insert device of the present invention with a length of up to 35 mm may remain in the upper fornix and one with a length of up to 25mm may remain in the lower fornix without causing discomfort.

Examples of ophthalmic drugs include antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalexin, oxytetracycline, chloramphenicol, kanamycin, rifampicin, tobramycin, gentamicin, erythromycin and penicillin; antibacterials such as sulfonomides, sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals including idoxuridine, trifluorothymidine, acyclovir, gancyclovir and interferon; non-antibiotic, anti-infection, anti-bacterial or anti-microbial drugs such as iodine based preparation triclosan, chlorhexidine,et al; anti-allergenics such as sodium cromoglycate, antazoline, methapyriline, chlorpheniramine, cetirizine and prophenpyridadine; anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone, dexamethasone 21-phosphate, fluorocinolone, medrysone, prednisolone acetate, fluoromethalone, betamethasone, and triamcinolone and non-steroidal agents such as indomethacin, diclofenac, flurbiprofen, piroxicam, ibuprofen and acetylsalicylic acid; decongestants such as phenylephrine, naphazoline and tetrahydrozoline: miotics and anticholinesterase such as pilocarpine, acetylcholine chloride, physostigmine, eserine,

carbachol, di-isopropyl fluorophosphate, phospholine iodine, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; sympathomimetics such as epinephrine; immunological drugs such as vaccines and immune stimulants; hormonal agents such as estrogens, estradiol, progestational, progesterone, insulin, calcitonin, parathyroid hormone and peptide, vasopressin, hypothalamus releasing factor; beta adrenergic blockers such as timolol maleate, levobunclol HCl and betaxolol Hcl; growth factors such as epidermal growth factor and fibronectin; carbonic anhydrase inhibitors such as dichlorphenamide, acetazolamide and methazolamide and other drugs such as prostaglandins, antiprostaglandins, and prostaglandin precursors; angiogenesis inhibitors such as steroids, angiostatin, antiproliferative agents such as flurouracil and mitomycin.

The drugs may be used in conjunction with a pharmaceutically acceptable carrier. Examples of pharmaceutically acceptable carriers include solids such as starch, gelatin, sugars, e.g., glucose, natural gums, e.g., acacia, sodium alginate, carboxy-methyl cellulose, polymers, e.g., silicone rubber; liquids such as sterile water, saline, dextrose, dextrose in water or saline; condensation products of castor oil and ethylene oxide liquid glyceryl triester of a lower molecular weight fatty acid; lower alkanols; oils such as corn oil, peanut oil, sesame oil, and the like, with emulsifiers such as mono- or di-glyceride of a fatty acid, or a phosphatide, e.g., lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence, of a suspending agent, for example, sodium carboxy-methylcellulose, sodium alginate, poly(vinylpyrrolidone), alone, or with suitable dispensing agents such as lecithin, polyclylic acid derivatives polyoxyethylene stearate. The carrier may also contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents.

The mechanism of controlled sustained drug release into the eye is for example diffusion, osmosis or bio-erosion and these mechanisms are described for example in U.S. Patent No. 4,186,184 and in "Therapeutic Systems" by Klaus Heilmann published by Georg Thieme, Stuttgart 1978.

The period of controlled sustained release is for example up to 7 to 14 days or

longer.

In one exemplary embodiment of the present invention utilising the diffusion mechanism, the configuration of the body of the insert device defines a reservoir for the drug which is in liquid or gel form. At least the lateral wall is a membrane permeable by diffusion so that the drug is released continuously at a controlled rate through the membrane into the tear fluid.

In one exemplary embodiment of the invention utilising the osmosis mechanism, the device comprises a transverse impermeable elastic membrane dividing the interior of the device into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable end wall of the device.

The first compartment contains a solute which cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form.

When the device is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

In one exemplary embodiment of the invention utilising the bierosion mechanism, the configuration of the body of the insert device is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the device with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

In another embodiment of the invention, there is employed a solid non-erodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by

gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

Examples of the materials for a permeable membrane for the diffusion mechanism include but are not limited to insoluble microporous materials of polycarbonates, polyvinyl chlorides, polyamides, copolymers of polyvinyl chloride and acrylonitrile, polyethylene, polypropylene, polysulphones, polyvinylidene fluorides, polyvinyl fluorides, polychloroethers, polyformaldehydes, acrylic resins, polyurethanes, polyimides, polybenzimadozoles, polyvinyl acetates, polyethers, cellulose esters, porous rubbers, cross-linked poly (ethylene oxide), cross-linked polyvinyl pyrrolidone, cross-linked poly (vinyl alcohol) and polystyrenes.

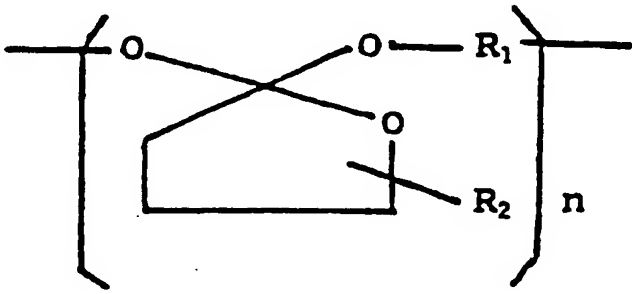
The drug in liquid or gel form for the diffusion mechanism comprises a diffusion medium which also serves as a pharmaceutical carrier and in which the active ingredient of the drug is dissolved or suspended; the active ingredient is preferably of no more than limited solubility in the medium. Examples of diffusion media include saline, glycerin, ethylene glycol, propylene glycol, water (which may also contain emulsifying and suspending agents), mixtures of propylene glycol monastearate and oils, gum tragacanth, sodium alginate, poly(vinyl pyrrolidone), polyoxyethylene stearate, fatty acids and silicone oil.

Examples of materials for an osmotic semi-permeable membrane include but are not limited to cellulose acetate and its derivatives, partial and completely hydrolysed ethylene-vinyl acetate copolymers, highly plasticized polyvinyl chloride, homo- and copolymers of polyvinyl acetate, polyesters of acrylic acid and methacrylic acid, polyvinyl alkyl ethers, polyvinyl fluoride; silicone polycarbonates, aromatic nitrogen-containing polymeric membranes, polymeric epoxides, copolymers of an alkylene oxide and alkyl glycidyl ether, polyurethanes, polyglycolic or polyacetic acid and derivatives thereof, derivatives of polystyrene such as poly(sodium styrenesulfonate) and poly (vinyl benzyltrimethyl-ammonium chloride), ethylene-vinyl acetate copolymers.

Examples of solutes which cannot pass through the semi-permeable membrane in an osmotic mechanism include but are not limited to water-soluble inorganic and

organic salts and compounds such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate. sodium carbonate, sodium sulfate, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium sulfate, potassium acid phosphate, calcium lactate, magnesium succinate, tartaric acid, acetamide, choline chloride, soluble carbohydrates such as sorbitol. mannitol, raffinose, glucose, sucrose and lactose.

Examples of bioerodible matrix materials include but are not limited to polyesters of the general formula -O-(W)-CO- and mixtures thereof, wherein W is a lower alkylene of 1 to 7 carbons and may include a member selected from the group of alkylenes of the formula $-CH_2-$, or $-CH-CH_2-$, and Y has a value such that the molecular weight of the polymer is from about 4.000 to 100,000. The polymers are polymerization-condensation products of monobasic hydroxy acid of the formula C_nH_{2n}, (OH) COOH wherein n has a value of 1 to 7, preferably 1 or 2 and the acid is especially lactic acid or glycolic acid. Also included are copolymers derived from mixtures of these acids. Bioerodible materials also include poly(orthoesters). These materials have the following general formula:



wherein R_1 is an alkylene of 4 to 12 carbons. a cycloalkylene of 5 to 6 carbons substituted with an alkylene of 1 to 7 carbons and an alkyleneoxy of 1 to 7 carbons, and R_2, is a lower alkyl of 1 to 7 carbons.

Other bioerodible matrix materials which may be employed include but are not limited to the following:

(1) Polyanhydrides such as poly(p-carboxyphenoxy) alkyl (e.g. p-carboxyphenoxypropane) or polymeric fatty acid dimer (e.g. poly-dodecanedioic acid) compounds and further copolymers with sebacic acid, or phthalic acid such as disclosed in Chasin et al., Polyanhdrides for Controlled Drug Delivery, Biopharm., February 1988, 33- 46; and Lee et al. (1988), The Use of Bioerodible Polymers and 5 fluorouracil in Glaucoma Filtration Surgery, Invest. Ophthalmol. Vis. Sci., 29, 1692-1697;

(2) Poly (alkyl-2-cyanoacrylates) such as poly (hexyl-2- cyancacrylate) as described by Douglas et al. (1987), Nanoparticles in Drug Delivery, CRC Crit. Rev. Therap. Drug Carr. Syst., 3, 233-261; and (3) Polyamino acids such as copolymers of leucine and methyl glutamate.

Further information on membrane and bioerodible materials is contained in U.S. Patents Nos. 3,828,777 and 4,186,184 and also the following references: Leong and Langer (1987), Polymeric Controlled Drug Delivery, Adv. Drug Del. Rev., 1, 199-233; and Smith et al. (1990), Bioerodible Polymers for Delivery of Macromolecules, Adv. Drug Del. Rev., 4, 343-357.

Examples of materials for use as non-erodible rods include but are not limited to polymers such as hydroxyethylmethacrylate and further co-polymers with methacrylic acid, methylmethacrylate, N-vinyl 2-pyrrolidone, allyl methacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, or 1,1,1 trimethylopropane trimethacrylate, and dimethyl diphenyl methylvinyl polysiloxane.

According to a second, independent, aspect of the present invention an ocular insert is provided, adapted for the controlled sustained release of drug(s), the insert having at least two distinct drug containing portions which:

(a) contain different drugs, and/or

(b) are adapted to release drug at different rates.

Preferably, the two or more drug containing portions are separated by a neutral portion or portions containing no drug and/or by some other barrier such as an impermeable membrane. In either case, the objective is to avoid mixing of the active

ingredients in the two or more regions, whether those ingredients be different drugs or different preparations or concentrations of the same drug.

Having two or more drugs contained in the insert in this way permits the use of synergistic, additive, supportive or complementary drugs for improved patient treatment in which the drugs are not mixed before release but which mix in the eye after independent release from the device. This avoids the need for regulatory studies on the mixture for antagonism and so on.

Having the same drug delivered at two different rates allows an initial high dose to be administered quickly, for example over a day or two, followed by the sustained release over a few weeks of a lower dose.

Combinations of these two approaches may also be envisaged.

A related aspect of the invention comprises a method of administering one or more drugs to a human or animal eye comprising inserting into the eye an ocular insert having at least two distinct drug containing portions which (a) contain different drugs and/or (b) are adapted to release drug at different rates.

Preferably, the said method also includes the step of leaving the insert in the eye for a period in excess of one day, preferably in excess of three days, more preferably in excess of one week.

Research carried out by the inventors shows that a multiple drug delivery ocular insert device releasing complementary or supportive or synergistic or additive drugs or drugs targeted at different pathological processes in the eye simultaneously but independently of each other, improves management of infectious and non-infectious eye diseases substantially, because combined drugs can:

a- reduce duration of treatment

b- require lower concentration of each drug resulting in reduction of toxic and adverse effects.

c- Improve efficacy of each drug

d- prevent or reduce development of resistance

e- allow treatment of two eye syndromes such as infection and inflammation with one device

f- reduce patient compliance problems

g- make substantial savings in the cost of treatment.

2.3- Examples:

The following are a few examples of the many applications of multiple drug delivery ocular insert devices.

a- Bacterial eye infection

An ocular insert device containing two antibiotics, one effective against gram positive bacteria and another effective against gram negative bacteria. Such a device would provide an important tool for early and effective treatment of ocular infections such as conjunctivitis, corneal ulcer and abscess or anterior uveitis following trauma or for treating for the presence of a foreign object in the eye and for preventing post-operative infection.

b- Inflammation of the eye; anterior uveitis

An ocular device containing two types of steroids; a lypophilic steroid which can penetrate corneal epithelium rapidly but is mostly retained in the cornea and a hydrophilic steroid which is slow in penetrating the corneal epithelium but rapidly passes through the cornea to the anterior chamber. The multiple drug device would greatly assist ophthalmologists in effective treatment of complicated conjunctivitis, keratitis, scleritis and anterior uveitis, particularly in preventing complications of these disorders.

c- Cytomegalovirus posterior uveitis.

Cytomegalovirus infection of the retina is a blinding complication of HIV infection. An ocular insert device containing an anti-viral compound and a steroid would be highly effective in halting the progress of uveitis and preventing its blinding complications.

d- Diabetic retinopathy

Retinopathy is a major blinding complication of diabetes. An ocular insert device containing an angiogenesis inhibitor and a relevant steroid which can act as an angiogenesis inhibitor as well as an anti-inflammatory agent, would provide a highly

effective tool for preventing development of neovascularisation and inflammation which are the major causes of diabetic retinopathy and its blinding sequelae.

e- Allergic conjunctivitis

An ocular insert device containing an antihistaminic compound and a steroid which is to be released at a very low concentration (to avoid the potential hazards of steroid) would be highly effective in controlling or preventing allergic diseases of the eye, the nose and possibly the upper respiratory tract. One device could potentially be fitted and remain in the eye for the entire season during which the allergic reaction is experienced.

f- Glaucoma

An ocular insert device containing two drugs; one to improve outflow of aqueous and another drug to reduce inflow of aqueous. Such a device would assist ophthalmologists particularly those who are working in primary eye care centres or clinics to manage intra-ocular pressure effectively at early stage, thus preventing development of blinding complications.

There are a number of other combinations of anti-glaucoma drugs which could usefully be incorporated in a multiple drug delivery ocular insert device for improved management of glaucoma.

The different drug's release rates can be adjusted to be optimal for each drug by independently tailoring the characteristics of the different drug bearing elements of the device.

It should be noted that this aspect of the invention does not require the device to have tapered end portions or anchoring protrusions, these being entirely optional features as regards the invention is its second aspect.

On the other hand, all the embodiments of tapered end portion devices described in relation to the tapered end portion devices according to the first aspect of the present invention may also incorporate the invention in this second aspect by forming distinct portions of each of these embodiments with distinct respective drugs for controlled release of those distinct drugs.

The two aspects of the invention may therefore be combined to provide a

flexible ocular insert device, adapted for the controlled sustained release of two or more drugs upon insertion into the upper or lower fornix of the eye, said device comprising an elongate body of a polymeric material said body containing a pharmaceutically active ingredient, said device having a length of at least 8mm and a maximum diameter not exceeding 1.9mm, wherein said device is sufficiently flexible to allow it to bend along the curvature of the eye within the upper or lower fornix upon being positioned so that the longitudinal axis of said device is generally parallel to the transverse diameter of the eyeball, said device being of a size and configuration such that, upon insertion into the upper or lower fornix, the device does not extend onto any visible portion of the eyeball, and in which at least two distinct portions of the device include respective distinct ones of said drugs.

Such multiple drug devices can be made by the same methods described in relation to the single drug release embodiments with suitable modifications. For example, they may be formed by injection molding in which each distinct material is forced into the device mold via distinct passageways so the distinct drug containing portions of the device are formed simultaneously as portions of a unitary device.

Alternatively, the distinct drug portions may be formed by separate molding processes as employed in a single drug delivery system and the portions joined together to form the final device, eg by use of a suitable adhesive.

Exemplary embodiments of the present invention according to both aspects will now be described with reference to the accompanying drawings of which:

Figure 1 is a diagrammatic sectional view of a prior art diffusional ocular insert device;

Figure 2 is a diagrammatic sectional view of a prior art osmotic ocular insert device;

Figure 3 is an enlarged diagrammatic sectional view of a prior art bioerodible insert device;

Figures 4a, 5a and 6a are diagrammatic views of a different flexible ocular insert devices according to first aspect of the present invention for insertion in the adult upper fornix;

Figures 4b, 5b and 6b are diagrammatic views of a different flexible ocular insert devices according to a first aspect of the present invention for insertion in the adult lower fornix;

Figures 7 and 8 are diagrammatic views of a different flexible ocular insert devices according to second, independent, aspect of the present invention;

Figure 9 is a diagrammatic view of a different flexible ocular insert device according to the second aspect of the present invention;

Figure 10 is a diagrammatic sectional view of the eye with an ocular insert device of the present invention installed in the upper and lower fornix;

Figure 11 is a diagrammatical front view of an eye with an ocular insert device of the present invention installed in the upper and lower fornix;

Figure 12 is a representation of the head of a patient with the location of the installed ocular insert device shown in dashed lines; and

Figure 13 is a diagrammatic view of the position of the installed ocular insert device in a closed eye; and

Figures 14 to 17 are graphs showing data on drug release rates of devices according to the present invention; and

The ocular inserts of Figures 4 to 9 will first be described in terms of their overall external configuration.

In the embodiment of Figures 4a, the device has two substantially right circular cone end-portions 2 which have a common base of diameter 1.4mm at the centre of the device and rounded apexes 3. Purely optional projections 4 are about 1mm wide and are formed about 0.2mm proud of the body of the device and spaced about 10mm apart.

The embodiment of Figure 5a, like that of Figure 4a, is in the shape of a joined pair of cones with base diameters of 1.4mm but in this case the cones are oblique circular cones 5 with the apexes 6 such as to provide the device with one straight, longitudinal edge 8. Optional projections 9, where present, may be positioned and dimensioned as shown by the dotted lines.

The insert may, alternatively, as shown in Figure 6a have a body comprising a

central cylindrical portion 10, for example, approximately 10mm long and 1.4mm in diameter and at each end an end portion 11, each in the form of a substantially right circular cone, 7.5mm in length with circular cross-sections reducing from 1.4mm diameter at the end adjacent the cylindrical portion to about 0.4mm at the outer extremity adjacent a rounder apex 12. It again may also include optional projections 13 as described in relation to the Figure 4a and 5a embodiments.

The devices of Figures 4b, 5b and 6b are configured as the devices shown in Figures 4a, 5a and 6a (with common features being the same reference numerals primed) but with the dimensions of the body reduced so as to be suitable for insertion in the lower fornix of an adult, the overall lengths of each device being 20mm and maximum diameter being 1.0mm. The optional toroidal projections 4, 9 or 13, when present, are as in the embodiments of Figures 4a, 5a and 6a, symmetrically located on the body of the device 10mm apart and 0.2mm proud of the body surface.

The embodiment of Figure 7 and 8 are configured as those of Figures 4a and 5a but differ in that the two halves release distinct drugs in use, whereas the former devices release only one drug. The different drug release portions of Figures 7 and 8 are indicated by the different shading. The device of Figure 6a as well as the lower fornix devices 5a, 5b and 6b can also be formed as a dual drug release device.

Figure 9 shows a further embodiment of the present invention in which the device has two similar body portions which are joined by a narrow cylindrical portion 22 of length 2mm and diameter 0.5mm. Each body portion is formed as a cylindrical portion 24 with a conical end portion 26 tapering to a 0.4mm radius apex at the extremity of the device. Each body portion 20 releases a different drug in use.

Figures 1 to 3 will now be described which illustrate various drug release arrangements employable with the present invention in all its aspects.

The prior art ocular insert device shown in Figure 1 comprises a circular cylindrical wall 40 of a microporous synthetic polymer membrane which is insoluble in tear fluid but is permeable by diffusion. The cylindrical wall 40 is closed by transverse planar end walls 42 which may be of the same microporous synthetic polymer membrane as the cylindrical wall 40 or alternatively may be impermeable.

The overall length of the device is 8 to 25mm or up to 35mm for the upper fornix and its external diameter 0.5-1.9mm.

The cylindrical wall 40 and the end walls 42 define a reservoir for a drug which diffuses through the membrane as described hereinbefore.

The prior art ocular insert device shown in Figure 2 comprises a circular cylindrical wall 110 closed by hemispherical domed end portions 112. The device also comprises, perpendicular to the axis of the cylindrical wall, an impermeable elastic membrane 114 dividing the interior of the device into a first compartment 116 and a second compartment 118. The cylindrical wall 110 comprises different materials as respectively do the end walls 112 so that the first compartment is bounded by a semi-permeable synthetic polymer membrane 120 and the elastic membrane 114 and the second compartment is bounded by an impermeable synthetic polymeric membrane 122 and the elastic membrane 114. There is an axial drug release aperture 124 in the membrane 122 at the domed end portion 112 thereof.

The first compartment 116 contains a solute and the second compartment provides a reservoir for a drug which is forced through the aperture 124 by the stretching of the elastic membrane 114 under osmosis as described hereinbefore.

The prior art ocular insert device shown in Figure 3 comprises a circular cylindrical body 210 with domed end portions 212. The device is constituted from a matrix of synthetic polymeric bioerodible material in which a drug is dispersed, being concentrated superficially of the matrix for controlled release therefrom as the matrix bioerodes.

The device having the configuration as shown in Figure 3 may also be constituted of a solid non-erodible material having pores and dispersed drug as previously discussed.

The overall length and diameter of each of the devices of Figure 2 and Figure 3 is the same as for the device of Figure 1.

The drug release techniques adopted by these prior art devices may all be used in relation to the devices of the present application.

The ocular insert device of the present invention may be installed in the fornix

by the method as follows.

METHOD OF INSERTING DEVICE IN THE UPPER AND LOWER FORNIX OF THE EYE

1 Method of inserting the device in the upper fornix

1.1 Anaesthetise the eye with a drop of a chosen anaesthetic.

1.2 Ask patient:

to sit on a chair.

move the head slightly backward (30^{o} approximately).

look down continuously.

1.3 Hold the device with suitable forceps in a slightly off centre position, leaving about 6-7mm of the device free beyond the lips of the forceps.

1.4 Lift the upper lid upward and backward to produce a gap of 3mm approximately between the lid and the eye.

1.5 Insertion into the fornix:

Insert first the one-half of the device with the free part into the gap between the lid and the eye.

Align the middle of the device with the middle of the upper fornix by moving the forceps to the left or right.

Push the forceps whilst still holding the device gently into the deep fornix until reaching the bottom of the fornix.

Drop the device in the deep fornix and remove the forceps, while holding the upper lid with a finger to the side of the forceps in order to prevent rejection of the device.

1.6 Ask the patient to close his/her eyes, then with the help of the head of the forceps and over the lid manoeuvre the device into the deep fornix. This is to ensure that the device is in the deep fornix.

1.7 Ask the patient to move his/her eye up, down and laterally 2 to 3 times. This is to ensure that the device is in the deep fornix and not moving with the eye movement.

2 Method of inserting the device in the lower fornix

2.1 Anaesthetise the eye with a drop of a chosen anaesthetic.

2.2 Ask patient:

to sit on a chair.

move the head slightly backward (30^{o} approximately).

look up continuously.

2.3 Hold the device with suitable forceps in a slightly off centre position, leaving about 5-6mm of the device free beyond the lips of the forceps.

2.4 Pull the lower lid down and forward to produce a gap of 3mm approximately between the lid and the eye.

2.5 Insertion into the fornix.

Insert first the one-half of the device with the free part into the gap between the lid and the eye.

Align the middle of the device with the middle of the lower fornix by moving the forceps to the left or right.

Push the forceps whilst still holding the device gently into the deep fornix until reaching the bottom of the fornix.

Drop the device into the deep fornix and remove the forceps whilst lifting the lower lid upward and inward against the forceps in order to prevent rejection of the device.

2.6 Ask the patient to close his/her eyes, then with the help of the forceps and over the lid manoeuvre the device into the deep fornix. This is to ensure that the device is in the deep fornix.

2.7 Ask the patient to move his/her eye up, down and laterally 2 to 3 times. This is to ensure that the device is in the deep fornix and not moving with the eye movement.

Upon installation, the ocular insert device will be positioned in the upper or lower fornix in one of the positions identified as "SDRD" as shown in Figures 10 to

13 of the drawings.

At least two protrusions should be present (where employed) with a view toward providing an overall symmetrical shape for the device. In the case where only two protrusions are employed, such protrusions should be evenly spaced relative to the length of the device so that the protrusions will be equidistant from their respective ends of the device. Where more than two protrusions are employed, it is important to provide a symmetrical arrangement with even spacing so as to achieve a uniform anchoring function along the length of the device.

The ocular insert device of the present invention may be formed with a polygonal or circular cross section, for example.

The drug loaded device can be formed by any of various known processes such as extrusion molding, injection molding, transfer molding or compression molding.

In carrying out the extrusion molding process, polymer material is, typically, blended with drug at ratios of drug up to 40% by weight on a cooled two roll mill and then fed into a screw drive extruder. By the action of the single flight screw with diminishing pitch and a length to diameter ratio of about 12:1 to 10:1, material is continuously forced out through a coin or plate die (port) with openings conforming to the shape and dimensions of the subject device (i.e. circular). For designs involving tube configurations, a mandrel held in place by a spider flange is positioned prior to the die. The continuous noodle is pulled via conveyer belt through a heated horizontal or vertical chamber (315 to 425 degrees C) to achieve vulcanization of the material. The final device is made by a cutting apparatus where the rods are cut to size. Additional modifications such as polishing the ends of the device can be accomplished.

In carrying out the transfer molding process, the blend of polymer material and drug is placed into a heated transfer press with an aluminum or stainless steel mold containing impressions of the proper shape and size. The material is forced into the mold at between 200 and 4000 psi. The mold itself is kept under 10 tons of clamp pressure. The mold is kept heated and under pressure at any of the following

conditions:

4 - 10 minutes	135 degrees C
15 minutes	100 degrees C
30 minutes	75 degrees C
2 hours	55 degrees C
5 hours	40 degrees C
24 hours	Ambient temperature (25 degrees C)

The mold is cooled, separated and the formed devices are then removed.

Multiple drug delivery devices according to the second aspect of the present invention are conveniently formed by injection molding with the distinct drug loaded materials being injected separately, but simultaneously, into the mold via respective passageways.

Silicone rubbers/elastomers may be employed as the material from which the devices are formed. The silicone rubbers/elastomers may be prepared as follows:

Silicone rubber prepared using dimethylsiloxane polymer or dimethyl and methylvinyl siloxane copolymers, reinforcing silica, platinum catalyst, inhibitor and siloxane crosslinker and other vulcanizing agents such as organic peroxides is either hand mixed, mixed on a two roll mill, or injection molded together with micronized drug (predominantly 10 micron particles or less). Drug is loaded into the polymer mixture at levels up to 40 weight percent of the total weight together with any other necessary excipients or release modifiers such as glycerin or sorbitol. Entrapped air within the mixture is removed by exposure to a vacuum of about 28 inches of mercury (94.8 kPa) for approximately 30 minutes. Drug is solidified within the polymer matrix by curing (vulcanizing) the mixture while being molded into the desired shape.

The devices may also be formed of bioerodible polymers prepared as follows:

Solid mixtures of bioerodible polymers (Polyhydroxyacids such as polylactic acid and polyglycolic acid, and polyhydroxybutyrate; Polyesters and polyorthoesters including cyclic ortho-esters with dials or diketeneacetals or diacids with dials or polyols; Polyanhydrides made from one or more of the following: p-carboxyphenoxy propane, p-carboxyphenoxy hexane, sebacic acid, dodecanedioic acid, 1,4-phenylenedipropionic acid, isophthalic acid, polypropylene fumarate and polypropylene maleate; Polypeptides; and Polycyanoacrylates) can be admixed with up to about 60% by weight of drug. The material can be compressed in aluminum or stainless steel molds situated in a Carver hydraulic press at 12 tons of pressure for at least 15 minutes at 100 degrees C.

As a further example, the devices may be formed of methacrylate hydrogels prepared as follows:

Hydrogels loaded with drug can be constructed from crosslinked methacrylate polymers which include compositions containing one or more of the following: 2-hydroxyethyl methacrylate (HEMA), ethylene glycol dimethacrylate, polymethylmethacrylate, methylmethacrylate, glycol monomethacrylate, ethylene monomethacrylates, glycol dimethacrylates, vinylpyrrolidone, methacrylic acid, divinylbenzene, and alkyldiol methacrylates, acrylamide, methylene bis acrylamide.

Various crosslinking percentages can be achieved by altering the ratios of the copolymers. For example a 40:1 weight ratio of acrylamide to methylene bis acrylamide produces a 2.5%. crosslinking. A buffered solution (pH 7-9) of the copolymers is made containing the desired crosslinking ratio. The final total polymer percentage can be varied from 1 to 25%. Drug is admixed into this solution. Suitable crosslinking free radical generator and catalyst (such as ammonium persulfate and tetra methyl ethylene diamine) is added. The mixture is poured into an appropriate mold with the desired shape. Polymerization occurs within 30 minutes.

These embodiments of the invention may employ the drugs and pharmaceutically acceptable carriers as previously described.

The following are specific examples which may be carried out in accordance with the present invention.

Example 1

One part of silastic MDX4-4210 curing agent (Dow Corning Corp, Midland, MI) is mixed with 10 parts of MDX4-4210 Silastic base elastomer (Dow Corning Corp, Midland, MI). The material is placed under vacuum of about 28 inches of mercury (94.8 kPa) for 30 minutes. Material is then transferred into a cylinder situated in a transfer press. The material is then forced into a 12 cavity aluminum mold heated to 135 degrees C which contained impressions of the ribbed device design and forced into the mold at a transfer pressure of 400 psi (2757.9 kPa) for 3.5 minutes. The mold itself is kept under 10 tons of clamp pressure. The mold is cooled, separated and the formed devices are removed. The devices are cleaned by soaking in isopropyl alcohol for approximately 5 minutes and allowed to air dry.

Example 2

One part of silastic MDX4-4210 curing agent (Dow Corning Corp, Midland, MI) is mixed with 10 parts of MDX4-4210 silastic base elastomer (Dow Corning Corp, Midland, MI). Oxytetracycline hydrochloride (Sigma Chemical Cc., St. Louis) in the amount of 10% by weight of the total mixture is thoroughly blended in with care taken to minimize entrapment of air. The material is placed under vacuum of about 28 inches of mercury (94.8 kPa) for 30 minutes. Material is then transferred into a cylinder situated in a transfer press. The material is then forced into a 12 cavity aluminum mold heated to 135 degrees C which contained impressions of the device design and forced into the mold at a transfer pressure of 400 psi (2757.9 kPa). The mold itself is kept under 10 tons of clamp pressure for 3.5 minutes. The mold was cooled, separated and the formed devices are removed.

Example 3

One part of Silastic MDX4-4210 curing agent (Dow Corning Corp, Midland, MI) is, mixed with 10 parts of MDX4-4210 Silastic base elastomer (Dow Corning Corp, Midland, MI). Oxytetracycline hydrochloride (Sigma Chemical Co., St. Louis)

in the amount of 20% by weight of the total mixture was thoroughly blended in with care taken to minimize entrapment of air. The material is placed under vacuum of about 28 inches of mercury (94.8 kPa) for 30 minutes. Material is then transferred into a cylinder situated in a transfer press. The material is then forced into a 12 cavity aluminium mold heated to 121 degrees C which contained impressions of the tapered, device design and forced into the mold at a transfer pressure of 800 psi (5515.8 kPa). The mold itself is kept under 10 tons of clamp pressure for 3.25 minutes. The mold was cooled, separated and the formed devices are removed.

Example 4

Silastic medical grade ETR elastomer Q7-4720 (Dow Corning Corp, Midland, MI) is prepared by first individually softening Part B and Part A of the elastomer on a cooled two-roll mill. The two components are then blended together in a 1:1 ratio on the two-roll mill. Material was then transferred into a cylinder situated in a transfer press. The material is then forced into a 12 cavity aluminum mold heated to 121 degrees C at a transfer pressure of 800 psi (5515.8 kPa). The mold itself is kept under 10 tons of clamp pressure for 3.25 minutes. The mold is cooled, separated and the formed devices are removed.

Example 5

Medical grade liquid silicone rubber Silastic Q7-4840 A/B (Dow Corning Corp, Midland, MI) is prepared by mixing equal portions of the A and B components. A vacuum of 29 inches of mercury (98.2 kPa) is applied to the mixture for 30 minutes to deair the material. The material is compression molded in an aluminum mold in a carver press for 15 minutes at 100 degrees C under 12 tons of pressure. The mold is cooled, separated, and the devices removed. The devices are cleaned by soaking in isopropyl alcohol for approximately 5 minutes and allowed to air dry.

Example 6

Silastic medical grade ETR elastomer LSR 76000 (Dow Corning Corp.,

Midland, MI) is prepared by first individually softening Part B and Part A of the elastomer on a cooled two-roll mill. The two components are then blended together in a 1:1 ratio on the two-roll mill. Oxytetracycline hydrochloride with or without USP grade dextrose premixed in various ratios is added incrementally into the blend to assure homogeneous distribution. Material is then transferred into a cylinder situated in a transfer press. The material is then forced into a 12 cavity aluminium mold heated to 121 degrees C at a transfer pressure of 800 psi (5515. 3 kPa). The mold itself is kept under 10 tons of clamp pressure for 3.25 minutes. The mold is cooled, separated and the formed devices are removed.

Example 7

For control devices not containing any protrusion beyond the core, simple rods were prepared as in Example 1 except using a mold with impressions of a the desired device shape.

Example 8

A study was carried out in which the device of the present invention was inserted into the upper or lower fornix of the eyes of human patients with no eye disease by the method described earlier in the application. Results are shown in Tables 1 to 5.

The configuration of the cylindrical device was as shown in Figure 6b and called the SDRD-3 device. The material employed was a solid silastic based material Nusil MED-4830, a medical grade elastomer. No drug was incorporated into the device.

This study was carried out in the eyes of human volunteers, rather than experimental animals since the size and depths of the upper or lower fornix of experimental animals are different from the human eye. In some animals, the presence and movement of nictitating membrane can dislodge the device.

A Retention in the Upper Fornix

The method of insertion into the upper fornix used in this study was as follows.

The volunteer was asked to sit down, hold his/her chin slightly up and to look down continuously throughout the exercise.

The eye was anaesthetized by a drop of Benoxenate (oxybuprocaine) hydrochloride 0.4% W/V (Smith & Nephew). The upper lid was separated from the globe by about 4 to 5 millimeters by holding the eyelashes and gently pulling the lid backward and upward. The device, held in the forceps, was centrally located at a midpoint between the nasal and temporal canthus and was pushed under the upper lid inward about 6 to 7mm. The tip of a finger was positioned in the middle of the eyelid just above the end of the forceps before the device was released and forceps removed. With the tip of a finger, or the upper end of the forceps, the device was gently pushed upward and toward the deep fornix. The manoeuvre was repeated twice more in each corner (canthus). The volunteer was asked to move the eye downward and upward three times.

The volunteer was advised.

(a) If he/she feels that the end of the device was near the inner or outer corner (nasal or temporal canthus) of the eye or feels irritation, he/she can push the device back to the middle of the fornix by closing the eye and looking down, then, with the tip of a finger gently press the corner of the eye.

(b) Repeat manoeuvre explained above once in the morning after waking up and once in the evening before sleeping.

(c) Avoid rubbing the eyes.

(d) It is not possible to visualize the device in the deep fornix but he/she may be aware of sensation in a corner of the eye, relieved by prodding the upper part of the lid with a finger tip after closing the eye.

No additional topical or systemic treatment was given to any of the volunteers. The volunteers were asked to report to the investigator if the device was rejected from the eye. The duration of retention planned for four weeks.

In this study, 25 volunteers with normal eyes were included.

The device was randomly inserted in the upper fornix of the left or right eye in the volunteers.

The period of retention in the upper fornix is shown in appended Tables 1 and 2. In 18 volunteers (72%), the device was retained for 1 week or more. All 18 volunteers retained the device for 28 days or longer before it was removed.

The period of retention of the present invention in comparison with the retention of the device presented in US-A-5,395,618 are shown in appended Table 3. The results show that the present device was retained for 28 days or more in the upper fornix of 72% of volunteers while the device was retained for 28 days or more in the upper fornix of between 14% and 47% of volunteers.

B Retention in the Lower Fornix

Twenty five volunteers with normal eyes were included. The device was randomly inserted in the lower fornix of the right or left eye in the volunteers.

The results of the study on the retention of the present device in the lower fornix are shown in appended Tables 4 and 5.

In 11 (44%) of volunteers, the device was retained in the lower fornix for 14 days or more. Of these, 9 volunteers (36%) retained the device for 28 days or more. In comparison, the device is retained in the lower fornix for 1 or 2 days only.

Example 9

Experiments were carried out to study release kinetics of the present invention.

In Figures 14 to 17, there are provided various graphs showing drug release data for materials that can be used to form devices of the present invention. In these studies a Nusil Med-4830 elastomer was employed and the release rate for efficacy is shown as well as results obtained when the device was loaded with fluorescein disodium and various excipients.

The data in Figures 14 to 17 show release rate from the device made of a Nusil MED-4830 loaded only with fluorescein disodium as a drug representative and release rates from the devices loaded with excipients in addition to fluorescein.

As shown in the graphs 15 and 16, devices loaded with Carbopol or hydroxypropylmethyl cellulose (HPMC) provided a highly desirable zero order or near zero order release kinetics. Figure 17 shows a graph release data in accordance with the present invention, in which loading the device with Carbopol and HPMC combined provided a long term release kinetic of zero order or near zero order for over a month period.

Example 10

In Table 6 and Figures 18 to 21 there are shown data graphs of the swelling rate of a particular elastomer employed in a device of the present invention. Swelling is caused by the migration of water into the polymer, dissolving the drug and causing the polymer to swell due to an osmotic effect as water forces the polymer outwardly. Such swelling can be desirable inasmuch as a device of the present invention may lock into place as it grows in size and facilitates diffusion of the drug. It has been found that when silicone materials are loaded with drugs and/or excipients they are particularly prone to swell in this manner. As indicated by the graphs, it is within the scope of the invention to select the initial dimensions of a device and, by selecting the proper combination of solid drugs and excipients, to provide for the desired final dimensions of the device after swelling.

Figure 18 shows that silicone elastomer alone does not swell when exposed to water.

In Figures 19 to 21 there are shown the measurements obtained with regard to swelling of a device of the present invention which has been loaded with carbopol, HPMC or combined carbopol and HPMC. At large drug loads, the device can swell so that both length and diameter are increased significantly. In view of this tendency to swell when drugs and/or excipients have been incorporated, there are several possible approaches: (1) start with a small rod that is initially inserted; (2) adjust the ratio of drug to release modifiers which will affect the rate of water diffusion into the device; and (3) adjust the amount of platinum catalyst to facilitate more complete cross-linking of the polymeric material which reduces the amount of swelling.

The data in appended Table 6 show physical properties, including % elongation and swelling for a device of the present invention prepared in various formulations with various amounts of Carbopol, HPMC or combined Carbopol and HMPC, or various amounts of oxytetracycline and dextrose.

Example 11

It is generally the case that antibacterial drugs are particularly effective against either the gram positive or gram negative group of bacteria. The present invention can provide simultaneous doses of drugs separately more active against each group so saving time and expense in determining which type of bacteria is present in the eye. The drugs may also be selected which also provide additive, synergistic or complementary effects when present together in the eye fluid.

Example 12

The approaches to the treatment of glaucoma fall, generally, into two categories; improving drainage from the anterior chamber or reducing production of the aqueous humour. It may not be known which is the primary cause of the ailment in which case the present invention may be used to provide dosage of different drugs each treating the different possible cause simultaneously.

While the ocular insert of the present invention has been described herein as particularly well suited for treatment of humans, it is also within the scope of the invention to employ the present invention in the treatment of other animals such as cows and horses for diseases such as pink eye and the like.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive. The scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

TABLE 1

RETENTION OF SDRD-3

(NEW SHAPE MEASURING 20 x 1^{MM})

IN THE UPPER FORNIX OF 25 ADULT VOLUNTEERS

WITH NORMAL EYES

Days SDRD-3 retained	Number retained	
	No	%
More than 1 day	22	88
More than 2 days	21	84
More than 3 days	20	80
More than 5 days	19	76
More than 6 days	18	72
28 days or more*	18	72
Total	25	100

* = The insert was removed after 28 days

TABLE 2

CUMULATIVE RETENTION OF SDRD-3

(NEW SHAPE MEASURING 20 x1 MM)

IN THE UPPER FORNIX OF 25 ADULT VOLUNTEERS

WITH NORMAL EYES

Weeks SDRD-3 retained	Number retained	
	No.	%
More than one week	18	72
More than two weeks	18	72
More than three weeks	18	72
Four weeks or more *	18	72
Total	25	100

* = The insert was removed after 28 days

TABLE 3

COMPARATIVE RETENTION OF SDRD-3 (NEW SHAPE MEASURING 20 X 1 MM) AND SDRD IN THE UPPER FORNIX OF ADULT HUMAN EYES

Studies		Type of Insert	Size (mm)	No. of Eyes Inserted	Duration and Number Retained (Weeks)							
					≥ 1 week		≥ 2 weeks		≥ 3 weeks		≥ 4 weeks	
					No	%	No	%	No	%	No	%
1	Islamabad, Pakistan 1998 * (New Shape)	SDRD-3 (Ribbed)	20 x 1	25	18	72	18	72	18	72	18	72
2	Karachi, Pakistan 1991 *	SDRD (Un-ribbed)	25 x 1.5	17	12	71	9	53	8	47	8	47
3	London, England 1992*	SDRD (Ribbed)	25 x 1.5	9	6	67	5	56	5	56	4	44
4	Karachi, Pakistan 1992 **	SDRD (Un-ribbed)	25 x 1.5	50	31	62	17	34	10	20	7	14
5	Karachi, Pakistan 1992 **	SDRD (Ribbed)	25 x 1.5	24	15	62	9	37	8	33	7	29

* In volunteers with normal eyes

** In volunteers with an eye ailment (mainly infection)

TABLE 4

RETENTION OF SDRD-3

(NEW SHAPE MEASURING 20 X 1 MM)

IN THE LOWER FORNIX OF 25 ADULT VOLUNTEERS

WITH NORMAL EYES

Days SDRD-3 retained	Number Retained	
	No	%
More than 1 day	23	92
More than 2 days	17	68
More than 3 days	13	52
More than 5 days	12	48
More than 6 days	11	44
More than 20 days	10	40
More than 24 days	9	36
28 days or more*	9	36
Total	25	100

TABLE 5

CUMULATIVE RETENTION OF SDRD-3

(NEW SHAPE MEASURING 20 x 1 MM)

IN THE LOWER FORNIX OF 25 ADULT VOLUNTEERS

WITH NORMAL EYES

WEEKS SDRD-3 Retained	Number Retained	
	No	%
More than one week	11	44
More than two weeks	11	44
More than three weeks	10	40
Four weeks or more *	9	36
Total	25	100

*The insert was removed after day 28

TABLE 6

Formulation	Rate of swelling of the device	
	Length (%)	Diameter (%)
Silicone elastomer only	0	0
Silicone elastomer + 5% Carbopol	0	0
Silicone elastomer + 20% HPMC	15	14
Silicone elastomer + 5% carbopol + 20% HPMX	15	14
Silicone elastomer + 15% Oxytetracyclin and 15% Dextrose	15	28
Silicone elastomer + 20% Oxytetracyclin and 20% Dextrose	15	17

CLAIMS

1. A flexible ocular insert device adapted for the controlled sustained release of a drug upon insertion into the upper or lower fornix of the eye, said device comprising an elongate body of a polymeric material including two end portions said body containing a pharmaceutically active ingredient, said device having a length of at least 8mm and a maximum diameter not exceeding 1.9mm, wherein said device is sufficiently flexible to allow it to bend along the curvature of the eye within the upper or lower fornix upon being positioned so that the longitudinal axis of said device is generally parallel to the transverse diameter of the eyeball, the device does not extend onto any visible portion of the eyeball, and in which each of said end portions is tapered towards the extremities of the device.

2. A device according to claim 1, in which the end portions are each in the form of a right circular cone.

3. A device according to claim 1, in which the end portions are each in the form of an oblique circular cone.

4. A device according to claim 1 in which the apex of each end portion is rounded.

5. A device according to claim 1, wherein the length of the device is from 8 to 25mm for use in the lower fornix to suit the eyes of different sizes such as infants, children and adults.

6. A device according to claim 1, wherein the length of the device is from 8 to 35mm for use in the upper fornix to suit the eyes of different sizes such as infants, children and adults.

7. A device according to claim 1, wherein the diameter of the device including any radial protrusions is from 0.5 to 1.9mm to suit the eyes of different sizes such as infants, children and adults.

8. A device according to claim 1, wherein the body is tubular and the mechanism of drug release is by diffusion through an outer wall of the device.

9. A device according to claim 1, wherein the mechanism of drug release is by osmosis.

10. A device according to claim 1, wherein the mechanism of drug release is bioerosion.

11. A device according to claim 1, wherein the mechanism of drug release is by diffusion including possible drug dissolution.

12. A device according to claim 1, wherein the polymeric material is a silicone elastomer.

13. A device according to claim 1, wherein the polymeric material is made of hydrogel components.

14. A device according to claim 1, wherein the polymeric material is a methacrylate or hydroxymethacrylate based material.

15. A device as claimed in claim 1 adapted for the controlled sustained release of two or more drugs upon insertion into the upper or lower fornix of the eye, said device having at least two distinct portions, the said portions including respective distinct ones of said drugs

16. A flexible insert device as claimed in claim 15 and in which said end portions are tapered towards respective extremities of the device.

17. A device according to claim 16, in which the end portions are each in the form of a right circular cone.

18. A device according to claim 16, in which the end portions are each in the form of an oblique circular cone.

19. A device according to claim 16 in which the apex of each end portion is rounded.

20. A device according to claim 16, wherein the length of the device is from 8 to 25mm for use in the lower fornix to suit the eyes of different sizes such as infants, children and adults.

21. A device according to claim 16, wherein the length of the device is from 8 to 35mm for use in the upper fornix to suit the eyes of different sizes such as infants, children and adults.

22. A device according to claim 16, wherein the diameter of the device including protrusions is from 0.5 to 1.9mm to suit the eyes of different sizes such as infants, children and adults.

23. A device according to claim 16, wherein the body is tubular and the mechanism of drug release is by diffusion through an outer wall of the device.

24. A device according to claim 16, wherein the mechanism of drug release is by osmosis.

25. A device according to claim 16, wherein the mechanism of drug release is biorerosion.

26. A device according to claim 16, wherein the mechanism of drug release is by diffusion including possible drug dissolution.

27. A device according to claim 16, wherein the polymeric material is a silicone elastomer.

28. A device according to claim 16, wherein the polymeric material is made of hydrogel components.

29. A device according to claim 16, wherein the polymeric material is a methacrylate or hydroxymethacrylate based material.

30. A method for the controlled sustained release of one or more drugs into the eye over a period of time comprising inserting a flexible ocular insert device according to claim 1 or 15 into position in the upper or lower fornix of the eye and allowing said device to remain in the fornix for drug release during said period of time.

Fig.1.
Prior Art

Fig.2.

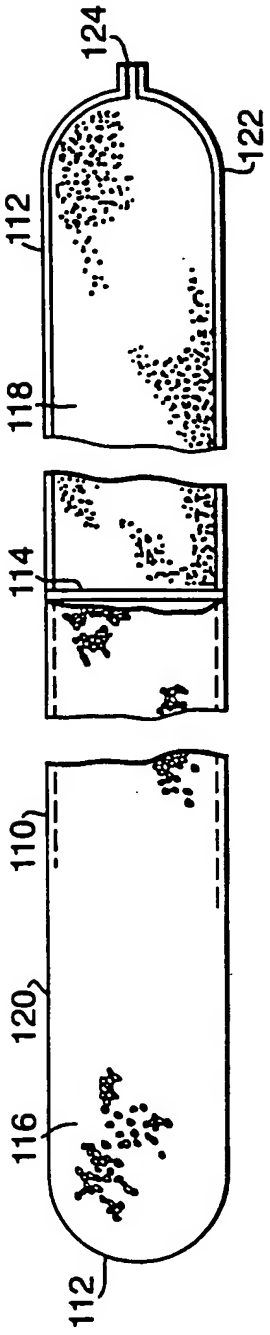


Fig.3.

Fig.4a.

Fig.4b.

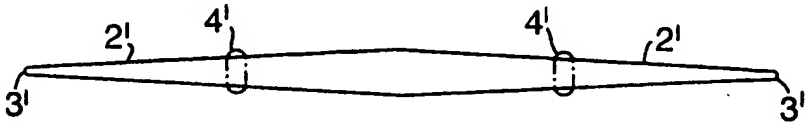


Fig.5a.

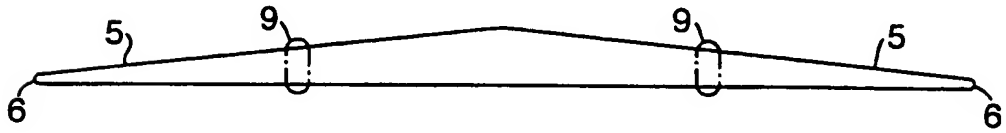


Fig.5b.

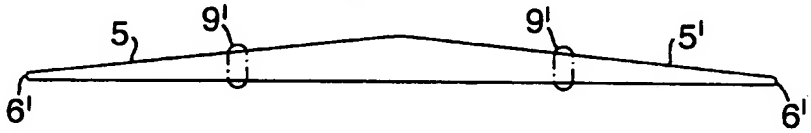


Fig.6a.

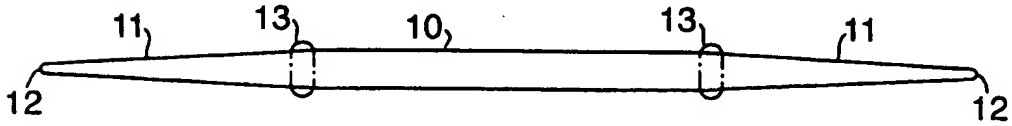


Fig.6b.

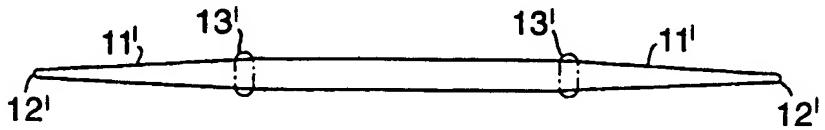


Fig.7.

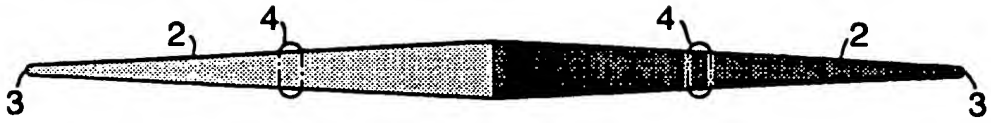


Fig.8.

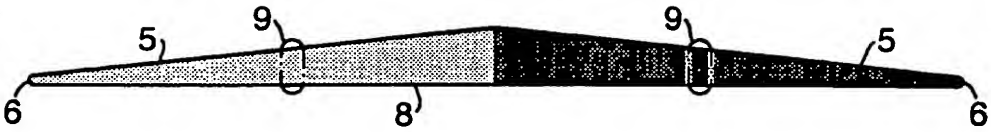


Fig.9.

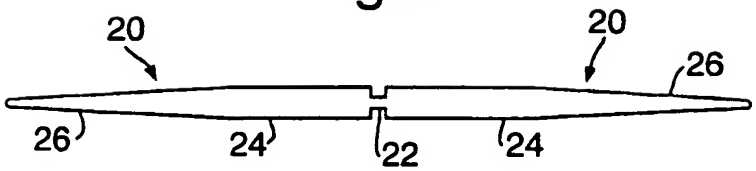


Fig.10.

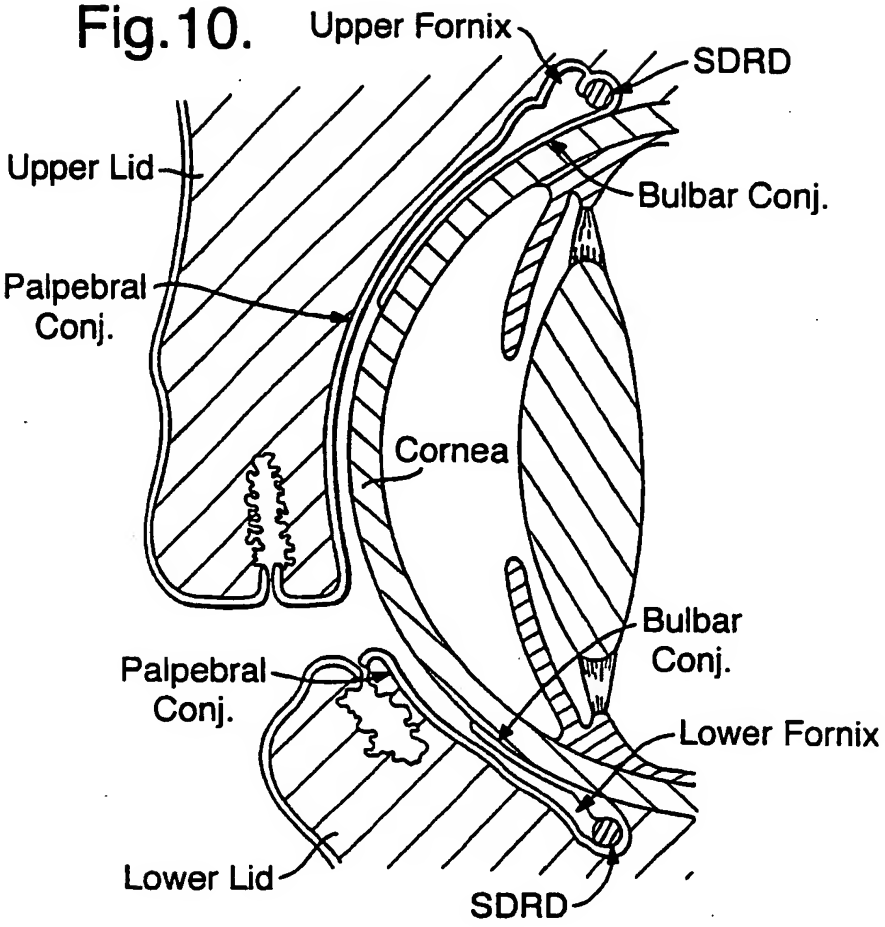

Upper Fornix
SDRD
Upper Lid
Bulbar Conj.
Palpebral Conj.
Cornea
Bulbar Conj.
Palpebral Conj.
Lower Fornix
Lower Lid
SDRD

Fig.11.

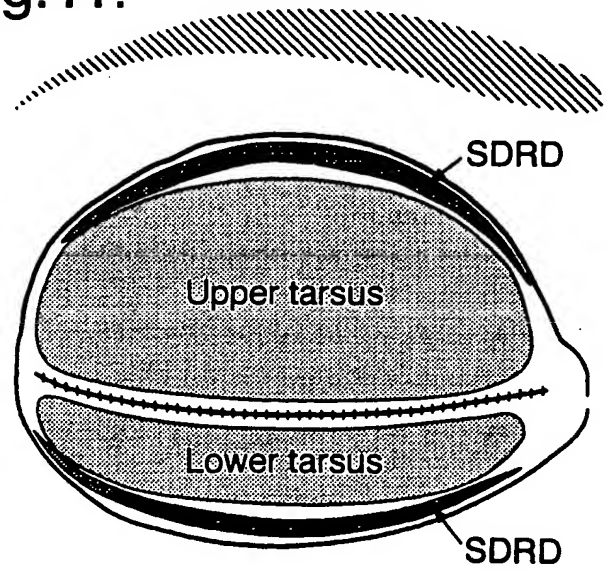

SDRD
Upper tarsus
Lower tarsus
SDRD

Fig.12.

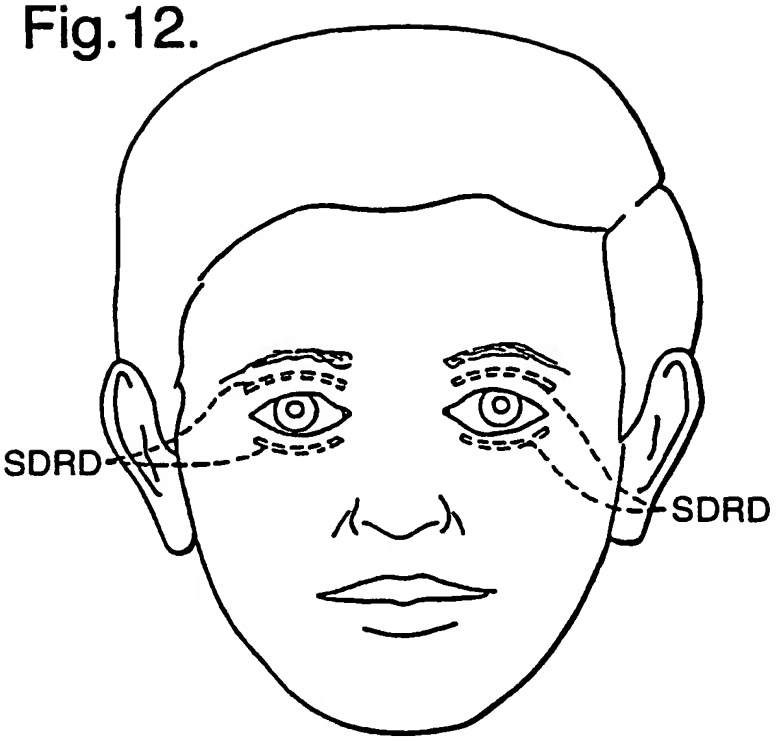


Fig.13.

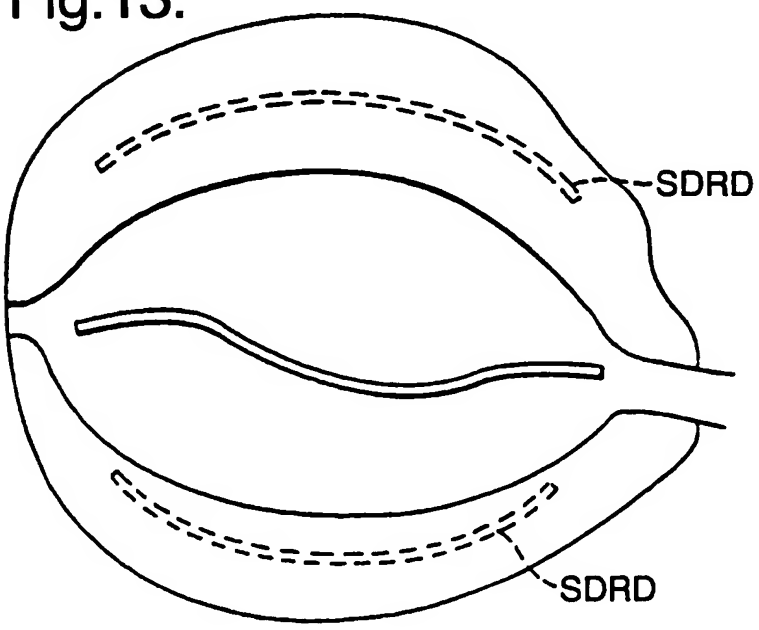


Fig.14.

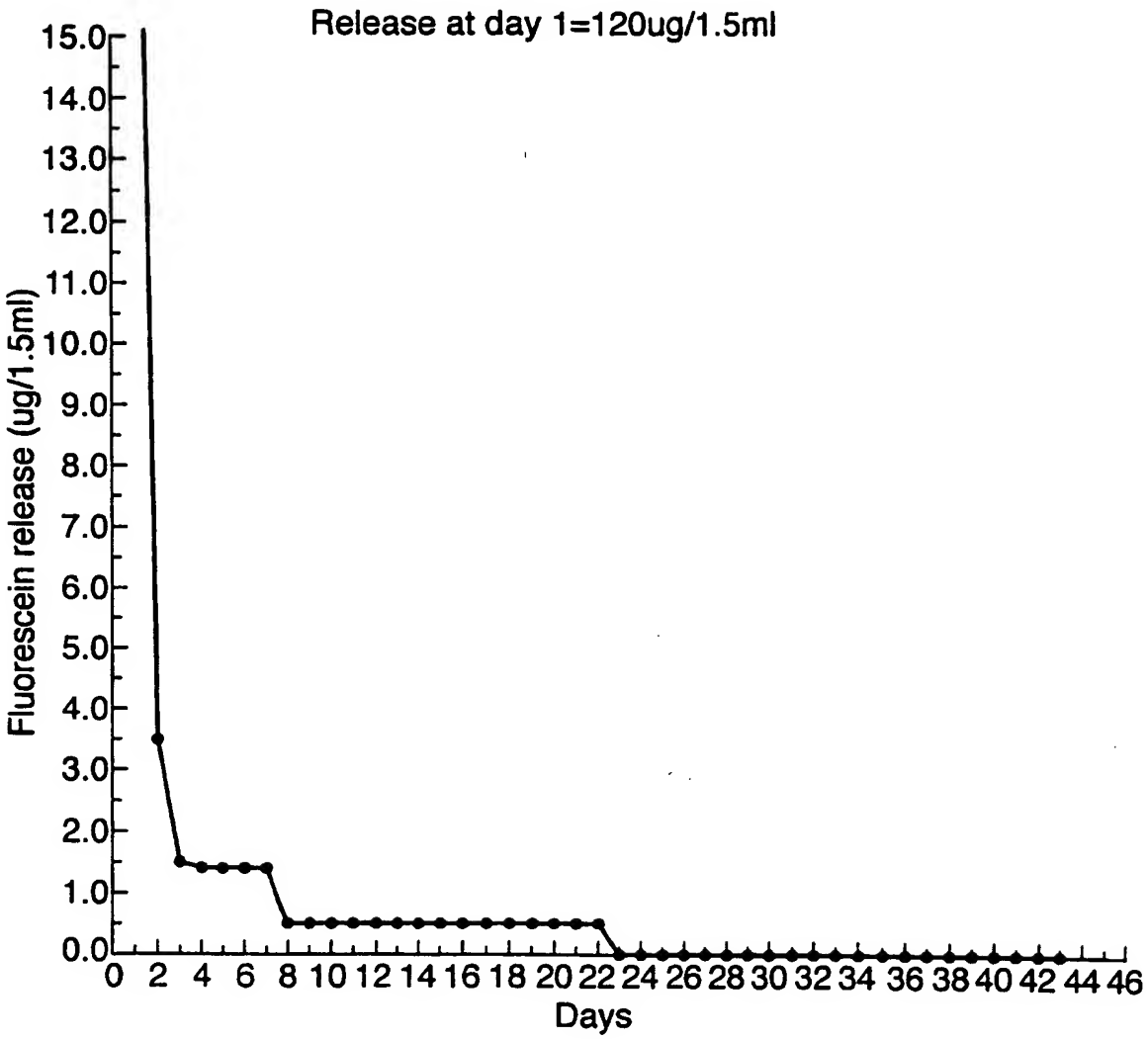

Release at day 1=120ug/1.5ml
Fluorescein release (ug/1.5ml)
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
Days

Fig.15.

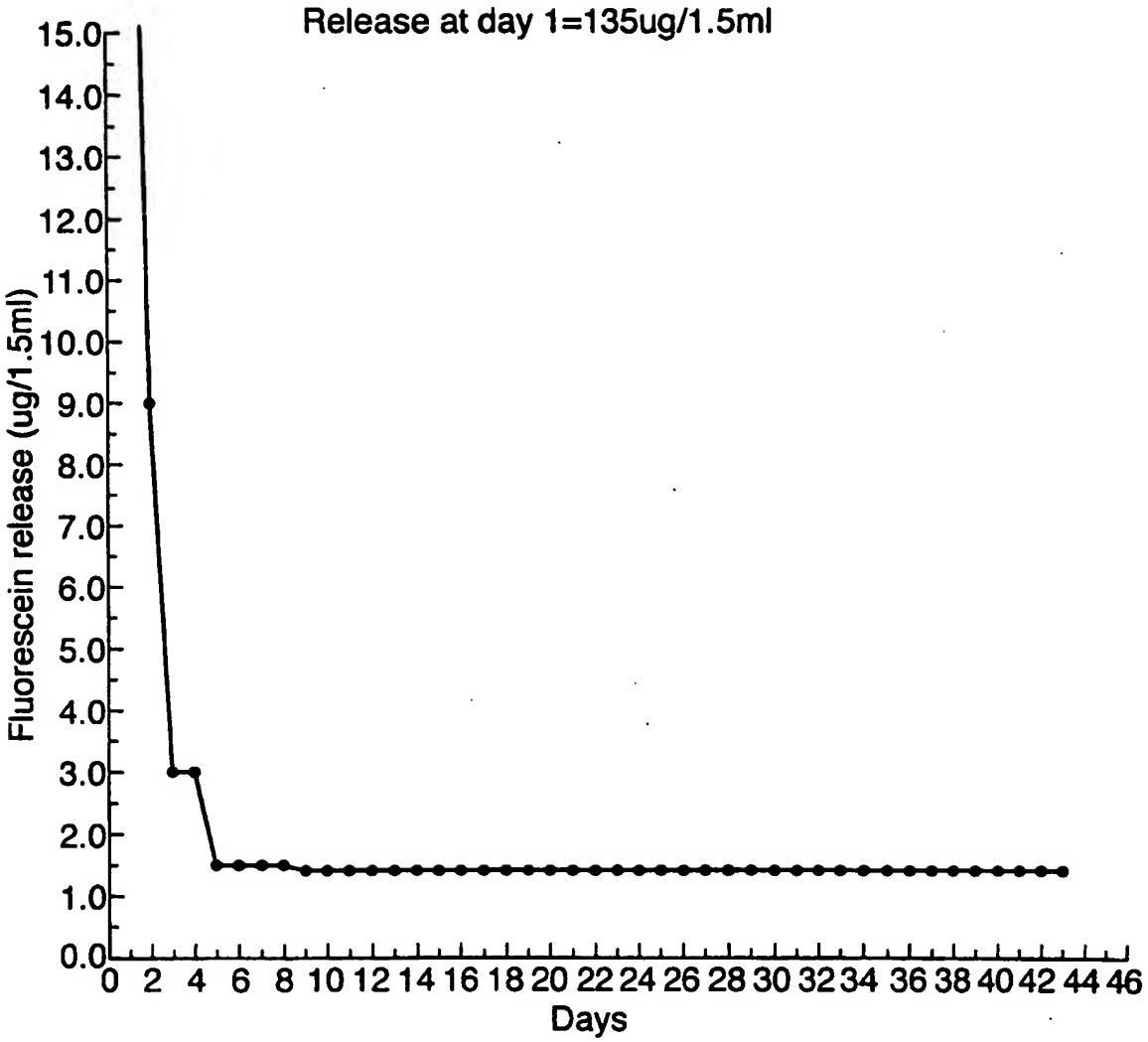

Release at day 1=135ug/1.5ml
Fluorescein release (ug/1.5ml)
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
Days

Fig.16.

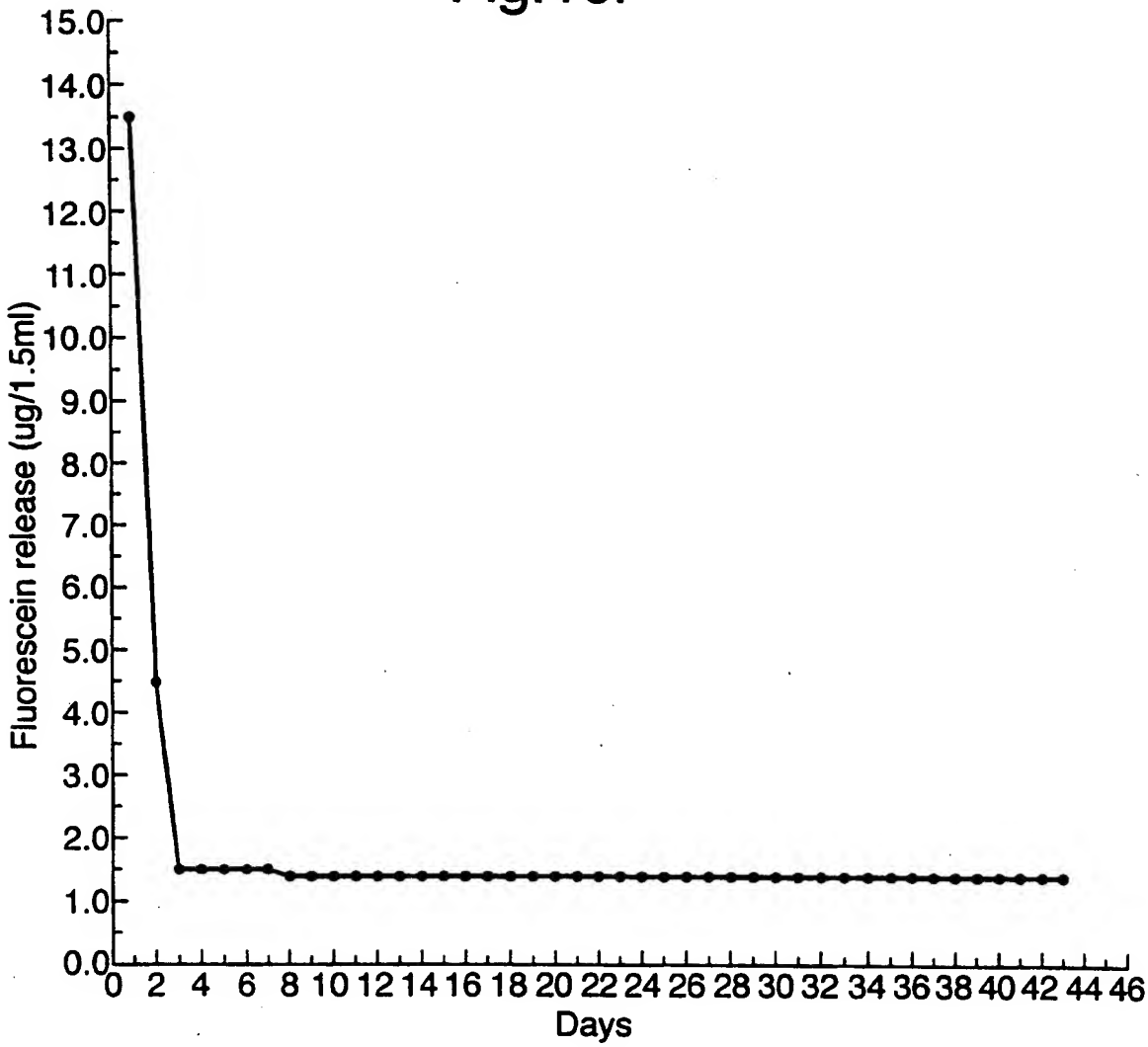

Fluorescein release (ug/1.5ml)
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
Days

Fig.17.

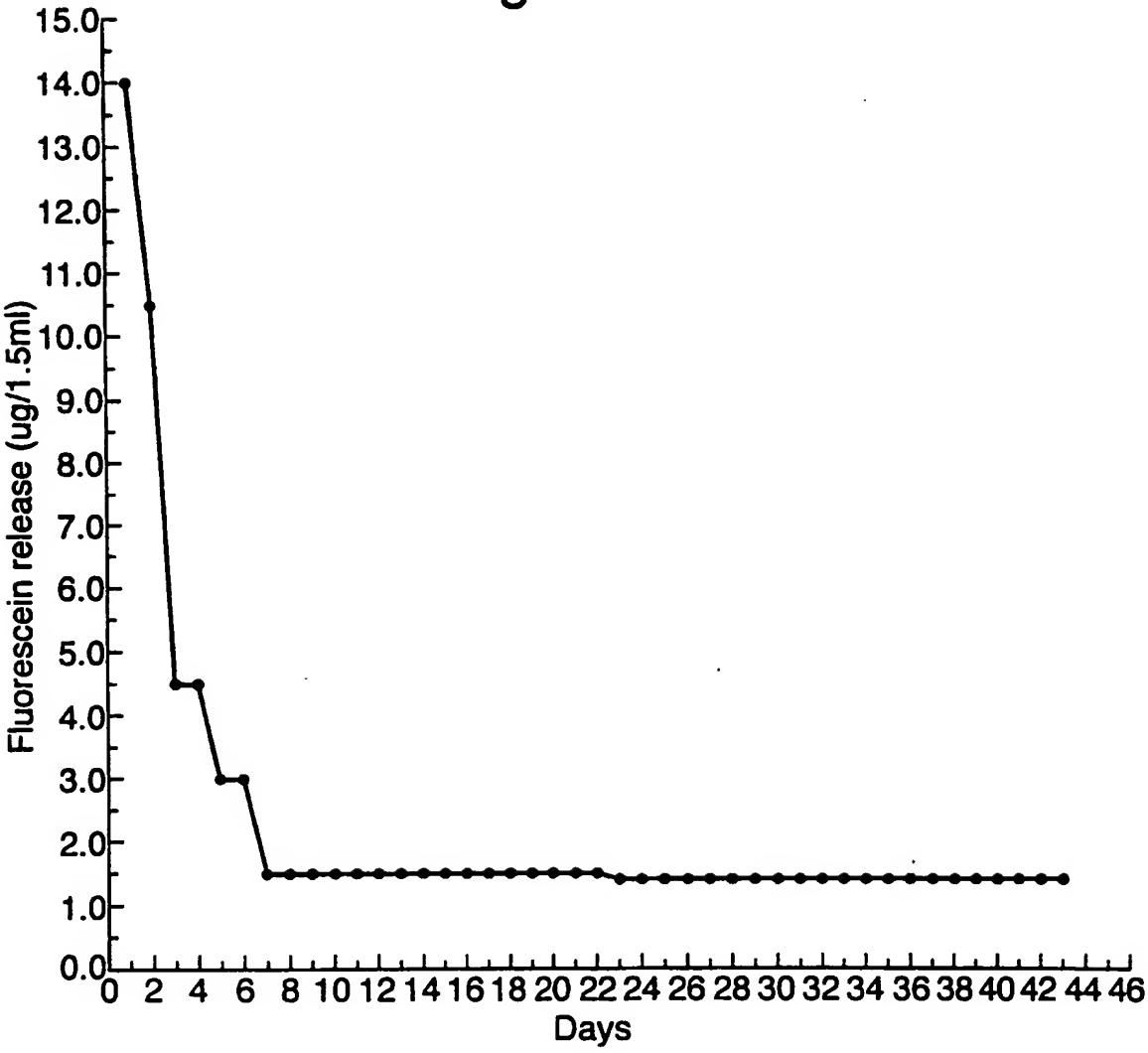

Fluorescein release (ug/1.5ml)
15.0
14.0
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46
Days

Fig.18.

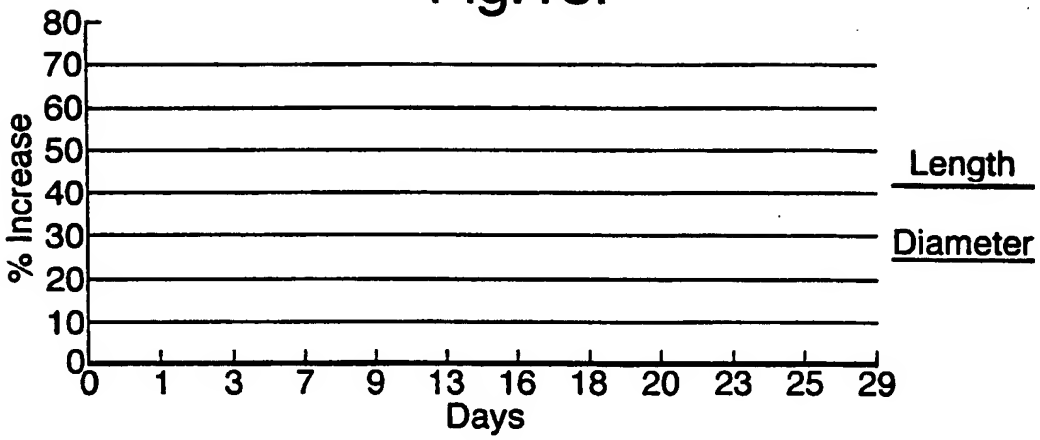

80
70
60
50
40
30
20
10
0
% Increase
0 1 3 7 9 13 16 18 20 23 25 29
Days
Length
Diameter

Fig.19.

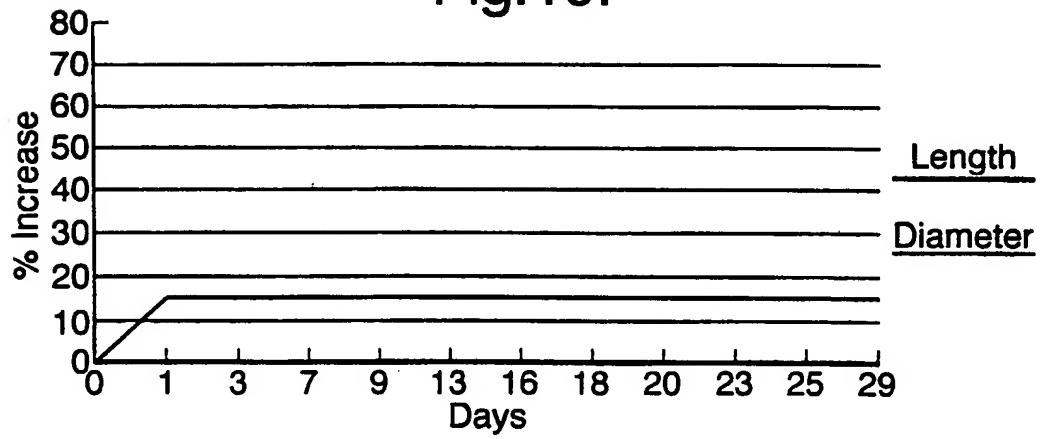

80
70
60
50
40
30
20
10
0
% Increase
0 1 3 7 9 13 16 18 20 23 25 29
Days
Length
Diameter

Fig.20.

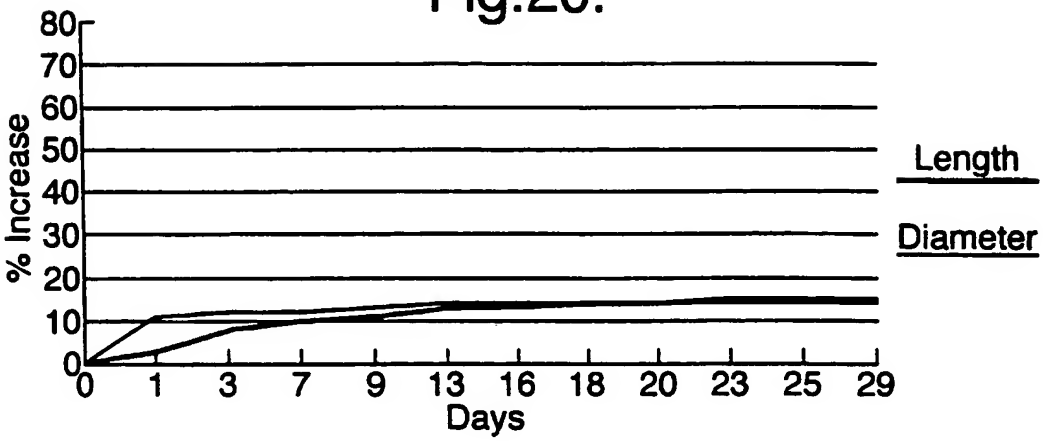
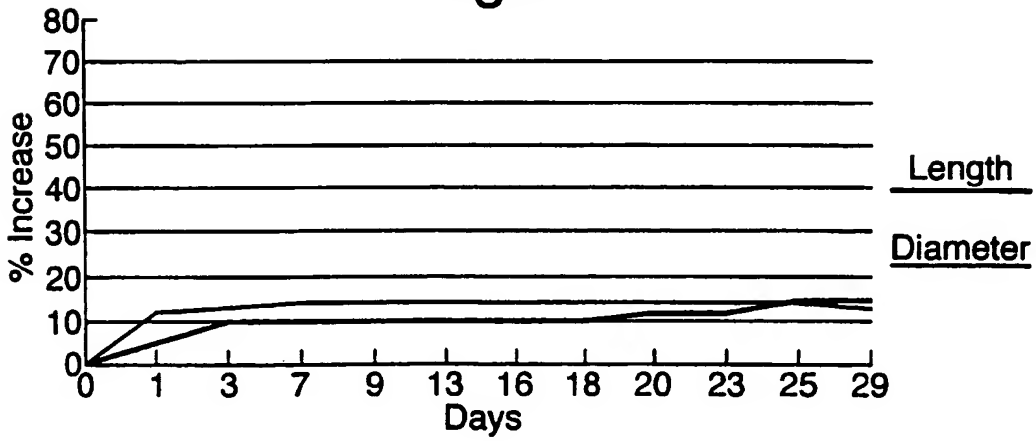

80
70
60
50
40
30
20
10
0
% Increase
0 1 3 7 9 13 16 18 20 23 25 29
Days
Length
Diameter

Fig.21.


80
70
60
50
40
30
20
10
0
% Increase
0 1 3 7 9 13 16 18 20 23 25 29
Days
Length
Diameter

INTERNATIONAL SEARCH REPORT

Interna. al Application No
PCT/GB 00/04224

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61F9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 01764 A (DAROUGAR SOHRAB ;BHATT PADMANABH PRAVINCHANDRA (US); GANTNER DAVID) 19 January 1995 (1995-01-19) page 4, line 25 -page 12, line 17 claims 1-56	1-30
Y	EP 0 262 893 A (DAROUGAR SOHRAB) 6 April 1988 (1988-04-06) the whole document	1-30
Y	GB 1 359 198 A (ALZA CORP) 10 July 1974 (1974-07-10) the whole document	1-30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2001	26/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna... ...l Application No
PCT/GB 00/04224

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